Fenofibrate enhances the radiosensitivity of human pancreatic cancer cells in vitro and in vivo

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Abstract: Radiotherapy plays a significant role in the management of pancreatic cancer. Enhancing the radiation sensitivity of pancreatic cells will be beneficial for pancreatic cancer patients. Fenofibrate is a specific ligand for nuclear receptor peroxisome proliferator-activated receptor alpha (PPARα), which is involved in multiple pathophysiological processes. Fenofibrate has been used for the treatment of diabetes, cardiovascular diseases and hyperlipidemia for a long time. Recently, fenofibrate has been shown to inhibit the growth of several kinds of cancer cells. However, the effect of fenofibrate on the radiosensitivity of pancreatic cancer and its underlying mechanism remain unknown. In this study, we found that fenofibrate inhibited the viability of human pancreatic cell lines (PANC1 and Patu8988) in a dose-dependent manner by an MTT assay. Pretreatment of 50 µM fenofibrate in PANC1 and Patu8988 cells potentiated the anticancer effect of radiation. In addition, pretreatment of fenofibrate combined with radiation significantly suppressed cell migration and invasion in pancreatic cancer cells. Moreover, fenofibrate sensitized PANC1 xenografts to irradiation with an enhancement factor 2.10 (P < 0.05). Microarray analysis revealed that fenofibrate plus radiation affected multiple genes, including TAOK2, JAK3, SLC39A7 (ZIP7) and TRPV1. Pathway analysis demonstrated that fenofibrate affected multiple pathways, including cytokine-cytokine receptor interaction, RIG-I-like receptor signaling pathway and transcriptional misregulation in cancer. Taken together, these results suggest that fenofibrate enhances the radiosensitivity of human pancreatic cancer cells in vitro and in vivo.

Keywords: Pancreatic cancer, radiotherapy, fenofibrate, radiosensitivity

Introduction

Pancreatic cancer is a highly lethal malignancy that has no witnessed major progress in early diagnostics and effective drugs to tame. It is expected to account for 17% of all cases diagnosed digestive system neoplasms and account for more than one-quarter (27%) of all digestive system neoplasms deaths, remaining the fourth most common cause of cancer-related death in the US in 2016 [1]. The incidence rates of pancreatic cancer increased from 2000 to 2011 both in the temporal trend analyses and age-standardized mortality rates for men in China [2]. Radiotherapy has been widely used in conjunction with surgery or/and chemotherapy in the management of pancreatic cancer [3]. However, the efficacy of radiotherapy is limited by the radioresistance of cancer cells [3, 4]. Despite significant technical advances of radiotherapy, identifying and defining novel drugs combinations to improve the response of radiation is still warranted [5].

Peroxisome proliferator-activated receptors are fatty acid activated transcription factors that belong to the nuclear hormone receptor [6-8]. Three PPAR isotypes (PPARα, PPARβ/δ and PPARγ) have been identified in vertebrates. These PPAR isotypes have a high degree of sequence homology but display distinct physiological and pharmacological functions depending on their target genes and tissue distribution. Activation of PPARα has been shown to play a key role in lipid catabolism, fatty acid oxidation, glucose homeostasis and the inflammatory process [7, 8]. Fenofibrate is known as a specific ligand for PPARα, involved in many
pathophysiological processes, such as inflammation, oxidative stress, and leukocyte endothelium interactions [9-11]. Fenofibrate has been used for the treatment of diabetes, cardiovascular diseases and hyperlipidemia for long time [12]. Recently, fenofibrate has been shown to inhibit the growth of several kinds of cancer cells, including glioma [13], lung [14] and pancreatic cancers [15]. However, the influence of fenofibrate on the radiosensitivity of pancreatic cancer cells and its underlying mechanisms remain unknown.

The aim of the present study was to investigate the effect of fenofibrate on the radiosensitive of pancreatic cancer cells. We found that fenofibrate at a dose of 50 µM displayed sufficient enhancement of antitumor and antimetastatic effects of radiation in human pancreatic cancer cells via complex mechanisms.

Materials and instruments

Cell culture

The human pancreatic cancer cell lines PANC1 and Patu8988 were cultured in Dulbecco’s modified Eagle’s medium (DMEM; HyClone, Logan, UT, USA) supplemented with 10% fetal bovine serum (FBS; HyClone, Logan, UT, USA), 100 U/mL penicillin and 100 µg/mL streptomycin. Cells were kept at 37°C in a humidified 5% CO₂ incubator. Fenofibrate (Sigma-Aldrich, St Louis, USA) was dissolved in dimethyl sulfoxide (DMSO, Sigma Aldrich, USA) and diluted by DMEM (without FBS) to different concentrations. Cells were treated with or without fenofibrate and irradiated 24 h later.

Irradiation

Cells were exposed to different dosages of ionizing radiation using X-ray linear accelerator (RadSource, Suwanee, GA, USA) at a fixed dose rate of 1.15 Gy/min.

Cell viability assay

The effect of fenofibrate and zinc ions on cell viability were monitored by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cells were cultured at a density of 2 × 10⁵ cells/well in 96-well plates with various concentrations of fenofibrate for 24 h prior to irradiation. After treatment, cells were incubated with 10 µL of 5 mg/mL of MTT solution at 37°C for 4 h. Then, the medium was removed and 100 µL of DMSO was added immediately prior to the assay. The optical density (OD) value for the absorbance was measured at 492 nm with a spectrophotometric plate reader (Bio-Rad Hercules, CA, USA). Cell viability rate (VR) was calculated as: (OD in experimental group/OD in control group) × 100%.

Clonogenic survival assay

Different densities (200-1,000) of cells were cultured in 6-well plates for 24 h prior to 0, 2, 4, 6 or 8 Gy irradiation, in the presence or absence of fenofibrate. After irradiation, cells were cultured in fresh medium for additional 10 days. Then, the cells were washed with phosphate buffered saline (PBS), fixed with methanol, stained with Giemsa (Beyotime, Haimen, China). Colonies consisting of more than 50 cells were counted. The surviving fractions were calculated by normalizing plating efficiency. Plating efficiency and surviving fractions were calculated and plotted as previously described [16]. SF (surviving fraction) = Number of colonies/(cells inoculated × plating efficiency). The survival curve was derived from a multi-target single-hit model: SF = 1-1-exp(-D/D₀)ⁿ. D₀ was defined as the dose that gave an average of one hit per target. The radiation sensitivity enhancement ratio (SER) was measured according to the multi-target single-hit model [16].

Wound healing migration and Matrigel invasion assay

Cells were seeded onto 6-well plates and allowed to form a confluent monolayer for 24 h. The cells were treated in the presence or absence of fenofibrate. After irradiation with 0 or 4 Gy, the cell monolayers were scraped with a conventional 200-µl pipette tip and an image was captured using a microscope (Olympus, Tokyo, Japan) immediately. The distance between the wound edges was observed again 24 h later.
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invading cells were removed. Invading cells were fixed with methanol, stained with 2% crystal violet. Invading cells were counted in 10 random microscopic fields under 200 × magnification.

Tumor growth delay

Four-week-old male outbred BALB/c mice were purchased from Shanghai SLAC Laboratory Animal Co., Ltd. (Shanghai, China), and kept under specific pathogen-free condition. PANC1 cells (1 × 10⁶ cells/per mouse) were subcutaneously injected into the hind limb of BALB/c nude mice. When tumors grew to 150 mm³ after inoculation on day 9, mice were randomized and divided into four groups (n = 5): 1) PBS group; 2) Radiation group; 3) Fenofibrate group; 4) Fenofibrate plus radiation group. Mice received intraperitoneal injections of fenofibrate (1.67 mg/kg) for 4 consecutive days in the third and fourth groups. Radiation was performed on tumors using X-ray linear accelerator (Clinac 2100 EX, Varian Medical Systems, Inc., Palo Alto, CA, USA) at a dose of 10 Gy with X-rays at 2 Gy/min on day 9. Tumor size was determined with a caliper every other day, and tumor volumes were calculated with the formula: tumor volume = (length (L) × (width (W))^2) × 0.52 [17]. Doubling time of tumor growth were calculated according to the protocol as previously described [18].

Microarray analysis

Microarray-based mRNA expression profiling was performed using the Roche-NimbleGen (135 K array) Array (Roche, WI). The microarrays contained approximately 45,033 assay probes corresponding to all of the annotated human mRNA sequences (NCBI HG-18, Build 36). Total RNA labeling and hybridization were performed using standard condition according to manufacturer instructions. Genes with fold-change of 2 or greater were subsequently subjected to pathway analysis using Ingenuity Pathway Analysis (Redwood City, CA, USA). KEGG pathway analysis was performed as previously described [19]. An adjusted P-value that is lower than 0.05 indicated a statistically significant deviation from the expected distribution, and thus the corresponding pathways were enriched in target genes. We analyzed all of the significantly up- or down-regulated mRNAs using KEGG pathway analyses.

Statistical analysis

Data are expressed as the mean ± standard error of the mean (SEM) of at least three independent experiments. Standard error bars were included for all data points. The data were first analyzed with the Kolmogorov-Smirnov test for data distribution normality. The data were then analyzed using Student's t test when only two groups were present or assessed by one-way analysis of variance (ANOVA) when more than two groups were compared. The P values for t-tests were performed by 2-tailed t-tests. Statistical analysis was performed using SPSS software (Release 19.0, SPSS Inc.). Data were considered significant if P < 0.05.
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Figure 2. Fenofibrate enhances radiation-induced anti-migration and anti-invasion in pancreatic cancer cells. In vitro scratch-wound healing assay was performed in (A, C) PANC1 and (B, D) Patu8988 cells. Cells were pretreated with fenofibrate or equivalent DMSO prior to radiation. Wound healing was observed 24 h after radiation. (E, F) PANC1 and (G, H) Patu8988 cells with indicated treatments were incubated for 24 hours after radiation to allow cells to migrate through the Matrigel and the cells that through the Matrigel were stained by crystal violet (× 400). Cell invasion rate of each group was calculated and plotted. Data are presented as the mean ± SEM (* P < 0.05, compared with the DMSO-treated control cells). Data are presented as the mean ± SEM of triplicate experiments (* P < 0.05, compared with DMSO-treated control cells).
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**Results**

*Fenofibrate enhances the antigrowth effect of radiation in pancreatic cancer cells*

To explore the role of fenofibrate in pancreatic cancer cell viability, an MTT assay was performed. As shown in Figure 1A, 1B, fenofibrate alone inhibited cell proliferation in both PANC1 and Patu8988 cells in a dose-dependent manner. The 50% inhibition concentration (IC50) of fenofibrate against PANC1 and Patu8988 cells was 233.22 µM and 228.15 µM respectively. To evaluate the ability of fenofibrate to enhance the anti-growth and anti-metastatic effects of radiation in pancreatic cancer cells, 50 µM fenofibrate was used for the following experiments, which resulted in over 80% cell viability.

To assess whether this dose of fenofibrate plus radiation modulates the viability of PANC1 and Patu8988 cells, cell viability assays were performed. As shown in Figure 1C, compared with radiation or fenofibrate alone group, 50 µM fenofibrate plus radiation significantly inhibited cell proliferation of both PANC1 and Patu8988 cells, the inhibitory effect of fenofibrate plus radiation was more pronounced. These results indicated that fenofibrate enhanced the antigrowth effect of radiation in pancreatic cancer cells.

*Fenofibrate reduces the migration and invasion of pancreatic cancer cells with or without radiation*

To investigate whether fenofibrate could significantly enhance the radiation-induced anti-migration and anti-invasion in pancreatic cancer cells, wound healing assays and cell invasion assays were performed. As shown in Figure 2A and 2B, compared with the control group, the migration ability of radiation group and fenofibrate group was modestly suppressed. Comparatively, the migration distance of fenofibrate plus radiation group was significantly shorter than that of radiation group and fenofibrate group. The effect of fenofibrate and radiation on pancreatic cancer metastasis was further investigated by Matrigel transwell assay. As shown in Figure 2E-H, compared with the control group, the invasion ability of radiation group was significantly suppressed. Whereas, compared with radiation group, fenofibrate plus radiation group significantly decreased the numbers of cells that penetrated the Matrigel-coated membrane. These results indicated that fenofibrate reduced migration and invasion of human pancreatic cancer cells with or without radiation.

*Fenofibrate increases the radiosensitivity of pancreatic cancer cells*

To investigate the effect of fenofibrate on radiosensitivity, clonogenic survival assay was performed. As shown in Figure 3A and 3B, the clo-
nogenic surviving fraction of PANC1 and Pan- 

To investigate the effect of fenofibrate on the xenograft growth of PANC1 cells in nude mice, tumor growth delay assays were performed. As shown in Figure 4A and 4B, compared with the control group, tumor volume was reduced by 33.3% in radiation group and 59.5% in fenofibrate plus radiation group. Besides, doubling time of tumor growth was calculated according to the protocol as previously described [13, 14]. As shown in Table 1, the doubling times for the tumor were 6.27 ± 0.19, 8.15 ± 0.52, 7.19 ± 0.29 and 11.13 ± 1.4 days in the control, radiation, fenofibrate and fenofibrate plus radiation group, respectively. The calculated enhancement factor of fenofibrate was 2.10 (P < 0.05). These results indicated that fenofibrate can enhance the radiosensitivity of pancreatic cancer in vivo.

Fenofibrate enhances the radiosensitivity of PANC1 cell via complex mechanisms

To illustrate the mechanisms for fenofibrate-mediated radiosensitization, microarray analysis of radiation alone and radiation plus fenofibrate was performed. A total of 2669 genes (1368 upregulated and 1301 downregulated genes) were identified with an expression differential of 2.0-fold or greater between the two groups (Figure 5A and Table 2). The differentially expressed genes included TAOK2, JAK3, SHISA2, OR4M1, SLC39A7 (ZIP7) and TRPV1. As expected, fenofibrate appeared to have modulated the radiosensitivity PANC1 cells via complex mechanisms. GO analysis revealed that fenofibrate affected multiple pathways, including calcium sensitive guanylate cyclase activator activity, prostaglandin-endoperoxide synthase activity and alkane 1-monooxygenase activity (Figure 5B). Pathway analysis demonstrated that fenofibrate affected multiple pathways, including cytokine-cytokine receptor interaction, RIG-I-like receptor signaling pathway and transcriptional misregulation in cancer (Figure 5C). These results suggested that fenofibrate might be a wide-spectrum regulator of gene expression in pancreatic cancer cells.

Discussion

Radiotherapy plays a significant role in the management of pancreatic cancer [5, 21, 22]. The antitumor effect of ionizing radiation is attributed to induction of single- and double-strand breaks in the DNA, resulting in the loss of cell proliferation. However, the efficacy of radiotherapy is limited by the radioresistance of pancreatic tumor cells [3]. It has been recognized that the conjugate of radiation and anti-
Fenofibrate enhances pancreatic cancer radiosensitivity

Figure 5. Predicted significant pathways involved in fenofibrate-mediated radiosensitization in pancreatic cells. A. Heatmap of gene expression between PANC1 cells after 4 Gy X-ray irradiation and 50 µM fenofibrate 24 h prior to 4 Gy X-ray irradiation. B. Gene Ontology (GO) classification of differentially expressed genes as follows: biological process, cellular component, and molecular function. C. Annotated KEGG pathways of differentially expressed genes.

Fenofibrate has been reported to inhibit cell proliferation in multiple types of cancers, such as colorectal [23]. Malignant chemotherapeutics has a survival benefit over radiation alone [23].
Table 2. Microarray analysis of gene expression changes between radiation and fenofibrate plus radiation in PANC1 cells (Top 20)

<table>
<thead>
<tr>
<th>No.</th>
<th>Gene Name</th>
<th>Fold Change</th>
<th>Chromosome</th>
<th>Description</th>
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</thead>
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<tr>
<td>1</td>
<td>TAOK2</td>
<td>26.29</td>
<td>chr16</td>
<td>Thousand-and-one amino acid kinase 2</td>
</tr>
<tr>
<td>2</td>
<td>JAK3</td>
<td>25.10</td>
<td>chr19</td>
<td>Janus kinase 3</td>
</tr>
<tr>
<td>3</td>
<td>SHISA2</td>
<td>24.22</td>
<td>chr13</td>
<td>Shisa family member 2</td>
</tr>
<tr>
<td>4</td>
<td>LCAP</td>
<td>22.34</td>
<td>chrX</td>
<td>Lung carcinoma-associated 10</td>
</tr>
<tr>
<td>5</td>
<td>CTNNB1</td>
<td>22.07</td>
<td>chr11</td>
<td>Catenin delta 1</td>
</tr>
<tr>
<td>6</td>
<td>MLLT3</td>
<td>21.31</td>
<td>chr9</td>
<td>Super elongation complex subunit</td>
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<tr>
<td>7</td>
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<td>chr11</td>
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<tr>
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<td>19.76</td>
<td>chr7</td>
<td>Retinol binding protein 2</td>
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<tr>
<td>9</td>
<td>UPP1</td>
<td>19.69</td>
<td>chr19</td>
<td>Domain containing ion transport regulator 1</td>
</tr>
<tr>
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<td>19.69</td>
<td>chr21</td>
<td>Long intergenic non-protein coding RNA 1547</td>
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<tr>
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<td>chr7</td>
<td>Hyaluronoglucosaminidase pseudogene1</td>
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<td>chr12</td>
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<tr>
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<td>chr3</td>
<td>Progestin and adipoq receptor family member 9</td>
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<td>chr17</td>
<td>Ovarian tumor suppressor candidate 2</td>
</tr>
<tr>
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<td>19.02</td>
<td>chr14</td>
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<tr>
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<td>Solute carrier family 39 member 7</td>
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<tr>
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<tr>
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<td>18.62</td>
<td>chr19</td>
<td>Microrna 1909</td>
</tr>
</tbody>
</table>

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</table>

No. Gene Name Fold Change Downregulated Chromosome Description
1 OR4M1 40.29 chr14 Olfactory receptor family 4 subfamily M member 1
2 SLC39A7 35.83 chr6 Solute carrier family 39 member 7
3 TRPV1 34.23 chr17 Transient receptor potential cation channel subfamily V member 1
4 MIR128-2 28.08 chr3 Microrna 128-2
5 SERPINA10 26.27 chr14 Serpin family A member 10
6 BA1 26.12 chr8 Brain-specific angiogenesis inhibitor 1
7 PARP3 25.49 chr3 Poly(ADP-ribose) polymerase family member 3
8 ZNF547 25.31 chr19 Zinc finger protein 547
9 PTPR1 25.24 chr1 Protein tyrosine phosphatase, receptor type U
10 SLC25A42 23.48 chr19 Solute carrier family 25 member 42
11 MIR33B 23.33 chr17 Microrna 33b
12 KCNN2 22.48 chr5 Potassium calcium-activated channel subfamily N member 2
13 MIR1909 22.02 chr19 Microrna 1909
14 B3GNT4 21.33 chr12 UDP-GlcNAc: betaGal beta-1,3-N-acetylglucosaminyltransferase 4
15 OPRD1 21.26 chr1 Opioid receptor delta 1
16 RIMKLA 20.85 Chr1 Ribosomal modification protein rimk like family member A
17 MS4A15 20.21 chr11 Membrane spanning 4-domains A15
18 FM04 19.90 chr1 Flavin containing monooxygenase 4
19 STK17A 19.28 chr7 Serine/threonine kinase 17a
20 COMP 19.27 chr19 Cartilage oligomeric matrix protein

Fenofibrate enhances pancreatic cancer radiosensitivity cells via complex mechanisms. Nude mice bearing PANC1 xenograft tumors confirmed the facilitation of antitumor effect of radiation by fenofibrate in vivo. Our results suggest the fea-
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as glioma, prostate, lung and pancreatic cancers [13, 14, 24, 25]. And several mechanisms such as metabolic catastrophe and oxidative stress, have been reported to be associated with the anticancer activity of fenofibrate [13, 14, 24, 25]. Recently, fenofibrate has also been demonstrated to modulate the radiosensitivity of cancer cells. It has been reported that fenofibrate sensitizes esophageal cancer cells to radiation [26]. Consistent with this report, fenofibrate enhances esophageal cancer cells to radiation by modulating cell cycle progression [27]. Here, we show that sensitizes pancreatic cancer cells to radiation in vitro and in vivo, which expands the potential application of fenofibrate in radiosensitization.

Several mechanisms have been reported to be involved in the pro-apoptotic role of fenofibrate. In esophageal cancer cells, fenofibrate decreases HIF-1α and vascular endothelial growth factor (VEGF) [26]. Another group demonstrated that fenofibrate induces G2/M arrest and suppresses expression of VEGF in esophageal cancer cells [27]. In pancreatic cancer cells, fenofibrate inhibited cell proliferation via activation of p53 mediated by upregulation of MEG3 [15]. These findings indicate a difference of fenofibrate between cancer cell types. To understand the landscape of fenofibrate-affected genes and pathways, we performed a microarray-based gene expression analysis. The results revealed that fenofibrate affects multiple genes that function in multiple pathways in pancreatic cancer cells, including TAOK2, JAK3 and ZIP7. For example, among fenofibrate-downregulated mRNAs, JAK3 is reported to be induced by radiation [28]. Inhibition of JAK3/STAT3 inhibits the proliferation and promotes the apoptosis of pancreatic cancer cells [29]. ZIP7 is reported to be involved in zinc homeostasis and the chemoresistance of breast cancer cells [30]. ZIP7 is the single member of ZIP family residing on the endoplasmic reticulum. Increased ZIP7 expression promotes the release of zinc to cytosol and activates the epidermal growth factor receptor (EGFR), protein kinase B (PKB, or AKT), mitogen-activated protein kinases (MAPKs) and any other growth factors increasing growth and invasion of cancer cells [30, 31]. Our study provides comprehensive clues that the radiosensitization of fenofibrate is likely to be mediated through combined mechanisms.

In summary, we demonstrated that fenofibrate at a dose of 50 µM displayed sufficient enhancement of antitumor and anti-metastatic effects of radiation in human pancreatic cancer

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Disclosure of conflict of interest

None.

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